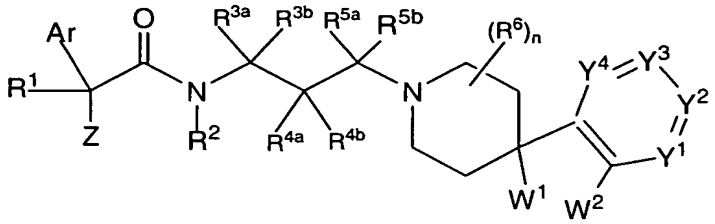
CLAIMS

1. An antagonist to melanin-concentrating hormone receptor which comprises as the active ingredient a piperidine derivative represented by the following general formula [I]



[I]

[in which R^1 stands for hydrogen, hydroxyl or optionally halogen-substituted lower alkyl, or R^1 and Z together form a 3 to 6-membered aliphatic carbocycle or aliphatic heterocycle, with the carbon atom to which they bind, said aliphatic carbocycle or aliphatic heterocycle optionally having a substituent group selected from Group α,

R^2, R^{3a}, R^{3b}, R^{5a} and R^{5b} each independently stands for hydrogen or optionally halogen-substituted lower alkyl,

R^{4a} and R^{4b} each independently stands for hydrogen, halogen, hydroxyl, or optionally halogen-substituted lower alkyl,

R^6 each independently stands for hydrogen, halogen or optionally halogen-substituted lower alkyl,

n stands for an integer of 1 – 8,

W^1 and W^2 either each stands for hydrogen, or W^1 and W^2 together form $-O-CH_2-$, $-CH_2-CH_2-$ or $-CH_2-O-$,

Z stands for lower alkyl or CY, or R^1 and Z together form a 3 to 6-membered aliphatic carbocycle or aliphatic heterocycle, with the carbon atom to which they bind, said aliphatic carbocycle or aliphatic heterocycle optionally having a substituent group selected from Group α,

CY stands for a cyclic group optionally having one, two or more substituent groups selected from Group α, which cyclic group is selected from

1) 3 to 10-membered aliphatic carbocyclic groups,

2) 3 to 10-membered aliphatic heterocyclic groups,

3) 5 or 6-membered aromatic carbocyclic groups, and

2) 5 or 6-membered aromatic heterocyclic groups,

Y^1, Y^2, Y^3 and Y^4 each independently stands for methylene which optionally has a substituent group selected from Group α, or nitrogen atom, with the proviso that not all of Y^1 to Y^4 are simultaneously nitrogen atoms, and

Ar stands for a mono- or bi-cyclic aromatic carbocyclic or aromatic heterocyclic group which may have one, two or more substituent groups selected from Group β]

or its pharmaceutically acceptable salt:

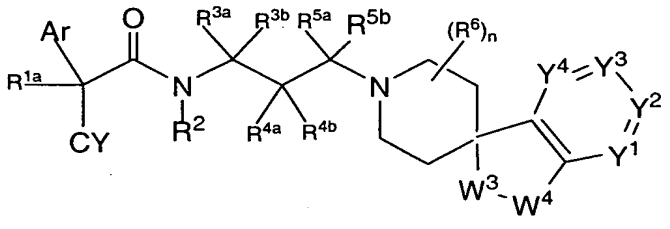
[Group α]

halogen, hydroxyl, amino, nitro, oxo, mono-lower alkylamino, di-lower alkylamino, optionally halogen-substituted lower alkyl, optionally fluorine-substituted lower alkyloxy, lower cycloalkyloxy, lower alkyloxycabonyl, (lower alkyloxycarbonyl)amino, (lower alkyloxycarbonyl) lower alkylamino, lower alkylcarbonyl, lower alkylcarbonyloxy, (lower alkylcarbonyl)amino, (lower alkylcarbonyl) lower alkylamino, carbamoyl, mono-lower alkylcarbamoyl, di-lower alkylcarbamoyl, carbamoylamino, mono-lower alkylcarbamoylamino, di-lower alkylcarbamoylamino, (mono-lower alkylcarbamoyl) lower alkylamino, (di-lower alkylcarbamoyl) lower alkylamino, carbamoyloxy, mono-lower alkylcarbamoyloxy, di-lower alkylcarbamoyloxy, lower alkylsulfonyl, lower alkylsulfonylamino, sulfamoyl, mono-lower alkylsulfamoyl, di-lower alkylsulfamoyl, sulfamoylamino, (mono-lower alkylsulfamoyl)amino, (di-lower alkylsulfamoyl)amino, (mono-lower alkylsulfamoyl) lower alkylamino and (di-lower alkylsulfamoyl) lower alkylamino.

[Group β]

nitro, aryloxy, lower cycloalkyl, lower cycloalkyloxy, lower alkylenedioxy, halogen, hydroxyl, optionally hydroxyl- or fluorine-substituted lower alkyl and optionally fluorine-substituted lower alkyloxy.

2. An antagonist as set forth in Claim 1, which comprises as the active ingredient a compound represented by the following general formula [I-1]



[I-1]

[in which R^{1a} stands for hydrogen, hydroxyl, or optionally halogen-substituted lower alkyl,

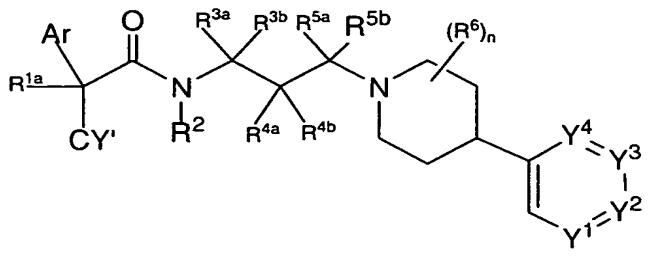
W^3 stands for –O– or $–CH_2–$,

W_4 stands for $–CH_2–$ or –O–,

with the proviso that W^3 and W^4 are not –O– at the same time, and

R^2, R^{3a}, R^{3b}, R^{4a}, R^{4b}, R^{5a}, R^{5b}, R^6, Y^1,Y^2, Y^3, Y^4, CY, Ar and n have the same significations as given in Claim 1].

3. An antagonist as set forth in Claim 1 which comprises as the active ingredient a compound represented by the following general formula [I-2]



[I-2]

[in which CY' stands for a substituent selected from the group consisting of pyrrolyl, imidazolyl, lower alkylimidazolyl, 4-nitroimidazolyl, triazolyl, lower alkyltriazolyl, tetrazolyl, pyridonyl, 2-oxo-1-piperidinyl, 2-oxo-1-piperazinyl, 4-lower alkyl-2-oxo-1-piperazinyl, 4-lower alkylsulfonyl-2-oxo- 1-piperazinyl and 4-lower alkylcarbonyl-2-oxo-1-piperazinyl, and

R^{1a}, R^2, R^{3a}, R^{3b}, R^{4a}, R^{4b}, R^{5a}, R^{5b}, R^6, Y^1, Y^2, Y^3, Y^4, Ar and n have the same significations as given in Claim 2].

4. The antagonist as set forth in Claim 1, in which R^1 is hydrogen, methyl or hydroxyl.

5. The antagonist as set forth in Claim 1, in which R^2 is hydrogen, methyl, ethyl, n-propyl or isopropyl.

6. The antagonist as set forth in Claim 1, in which R^{3a} and R^{3b} are hydrogen atoms.

7. The antagonist as set forth in Claim 1, in which R^{4a} and R^{4b} are selected from the group consisting of hydrogen, fluorine and hydroxyl.

8. The antagonist as set forth in Claim 1, in which R^{5a} and R^{5b} are hydrogen or methyl.

9. The antagonist as set forth in Claim 1, in which R^6 is selected from the group consisting of hydrogen, fluorine and methyl.

10. The antagonist as set forth in Claim 1, in which Y^1, Y^2, Y^3 and Y^4 are selected from the group consisting of –CH–, –CF–, $-C(NHCOCH_3)-$, $-C(NHCOC_2H_5)$ – and –N–.

11. The antagonist as set forth in Claim 1, in which the rings in the cyclic groups represented by CY are selected from the group consisting of cyclopentane ring, cyclohexane ring, pyrrolidine ring, morpholine ring, piperazine ring, piperidine ring, benzene ring, dihydropyridine ring, pyridine ring, pyrazine ring, pyrimidine ring, pyrrole ring, pyrazole ring, imidazole ring, triazole ring, tetrazole ring, oxazole ring, oxadiazole ring, oxazolidine ring and thiazole ring.

12. The antagonist as set forth in Claim 1, in which CY is a substituent selected from the group consisting of phenyl, 4-fluorophenyl, 4-chlorophenyl, 3,4-difluorophenyl, 4-methoxyphenyl, 4-tolyl, 4-trifluoromethylphenyl, pyridinyl, pyridin-3-yl, pyrazinyl, pyrimidinyl, 6-fluoropyridin-3-yl, 2-fluoropyridin-4-yl, 6-trifluoromethylpyridin-3-yl, 6-methoxypyridin-3-yl, pyrrol-1-yl, pyrazolyl, imidazolyl, 2-methylimidazolyl, 4-methylimidazolyl, 1,2,3-triazol-1-yl, 4-methyl-1,2,3-triazol-1-yl, 1,2,4-triazol-1-yl, 1,2,3,4-tetrazol-1-yl, 1,2,3,4-tetrazol-2-yl, oxazolyl, oxadiazolyl, thiazolyl, pyrrolidin-1-yl, piperidinyl, morpholinyl, dihydropyridinyl, 2-piperidon-1-yl, 2-pyridon-1-yl, 2-pyrrolidon-1-yl, oxazolidin-2-on-1-yl, 4-methanesulfonyl-piperazin-2-on-1-yl, cyclopentyl and cyclohexyl.

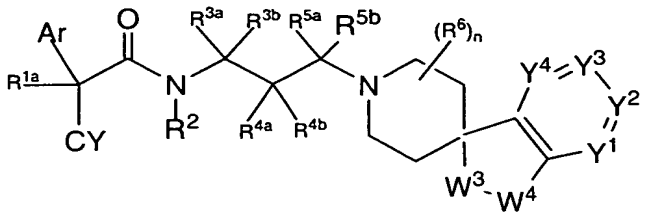
13. The antagonist as set forth in Claim 1, in which the aromatic ring in mono- or bi-cyclic aromatic carbocyclic group or aromatic heterocyclic group represented by Ar is selected from the group consisting of benzene ring, pyridine ring, pyrazine ring and pyrimidine ring.

14. The antagonist as set forth in Claim 1, in which Ar is a substituent selected from the group consisting of phenyl, 4-fluorophenyl, 3,4-difluorophenyl, 4-chlorophenyl, 4-methoxyphenyl, 4-tolyl, 4-trifluoromethylphenyl, pyridinyl, 6-fluoropyridin-3-yl, 6-trifluoromethylpyridin-3-yl, 6-methoxypyridin-3-yl, pyrazinyl and pyrimidinyl.

15. Preventing or treating agents of metabolic disorders represented by obesity, diabetes, hormone disorder, hyperlipidemia, gout, fatty liver, hepatitis and cirrhosis; cardiovascular disorders, represented by stenocardia, acute or congestive heart failure, myocardial infarction , coronary atherosclerosis, hypertension, renal diseases and electrolyte abnormality; central nervous system or peripheral nervous system disorders represented by bulimia, emotional disturbance, depression, anxiety, epilepsy, delirium, dementia, schizophrenia, attention-deficit hyperactivity disorder, memory impairment, sleep disorders, cognitive failure, dyskinesia, paresthesias, smell disorders, morphine tolerance, drug dependence and alcoholism; reproductive disorders represented by infertility, preterm labor and sexual dysfunction; digestive disorders; respiratory disorders; cancer or pigmentation, which comprise the antagonists as set forth in Claims 1 – 14 as the active ingredient.

16. Preventing or treating agents as set forth in Claims 15, which are preventing or treating agents for obesity.

17. Piperidine derivatives which are represented by the general formula [I-1]:



[I-1]

[in which R^{1a}, R^2, R^{3a}, R^{3b}, R^{4a}, R^{4b}, R^{5a}, R^{5b}, R^6, Y^1, Y^2, Y^3, Y^4, W^3, W^4, CY, Ar and n have the same significations as given in Claim 2] or their pharmaceutically acceptable salts.

18. Compounds or their pharmaceutically acceptable salts as set forth in Claim 17, in which R^{1a} is hydrogen, methyl or hydroxyl.

19. Compounds or their pharmaceutically acceptable salts as set forth in Claim 17, in which R^2 is hydrogen, methyl, ethyl, n-propyl or isopropyl.

20. Compounds or their pharmaceutically acceptable salts as set forth in Claim 17, in which both R^{3a} and R^{3b} are hydrogen atoms.

21. Compounds or their pharmaceutically acceptable salts as set forth in Claim 17, in which R^{4a} and R^{4b} are selected from the group consisting of hydrogen, fluorine and hydroxyl.

22. Compounds or their pharmaceutically acceptable salts as set forth in Claim 17, in which R^{5a} and R^{5b} are hydrogen or methyl.

23. Compounds or their pharmaceutically acceptable salts as set forth in Claim 17, in which all R^6 are hydrogen atoms.

24. Compounds or their pharmaceutically acceptable salts as set forth in Claim 17, in which Y^1, Y^2, Y^3 and Y^4 are selected from the group consisting of –CH–, –CF–, $-C(NHCOCH_3)-$, $-C(NHCOC_2H_5)-$ and –N–.

25. Compounds or their pharmaceutically acceptable salts as set forth in Claim 17, in which the rings in the cyclic groups represented by CY are selected from the group consisting of cyclopentane ring, cyclohexane ring, pyrrolidine ring, morpholine ring, piperazine ring, piperidine ring, benzene ring, dihydropyridine ring, pyridine ring, pyrazine ring, pyrimidine ring, pyrrole ring, pyrazole ring, imidazole ring, triazole ring, oxazole ring, oxadiazole ring, tetrazole ring, oxazolidine ring and thiazole ring.

26. Compounds or their pharmaceutically acceptable salts as set forth in Claim 17, in which CY is a substituent selected from the group consisting of phenyl, 4-fluorophenyl, 4-chlorophenyl, 3,4-difluorophenyl, 4-methoxyphenyl, 4-tolyl, 4-trifluoromethylphenyl, pyridinyl, pyridin-3-yl, pyrazinyl, pyrimidinyl, 6-fluoropyridin-3-yl, 2-fluoropyridin-4-yl, 6-trifluoromethylpyridin-3-yl, 6-methoxypyridin-3-yl, pyrrol-1-yl, pyrazolyl, imidazolyl, 2-methylimidazolyl, 4-methylimidazolyl, 1,2,3-triazol-1-yl, 4-methyl-1,2,3-triazol-1-yl, 1,2,4-triazol-1-yl, 1,2,3,4-tetrazol-1-yl, 1,2,3,4-tetrazol-2-yl, thiazolyl, pyrrolidin-1-yl, piperidinyl, 2-piperidon-1-yl, 2-pyridon-1-yl, 2-pyrrolidon-1-yl, oxazolidin-2-on-1-yl, 4-methanesulfonyl-piperazin-2-on-1-yl, cyclopentyl and cyclohexyl.

27. Compounds or their pharmaceutically acceptable salts as set forth in Claim 17, in which the aromatic ring in mono- or bi-cyclic aromatic carbocyclic group or aromatic heterocyclic group represented by Ar is selected from the group consisting of benzene ring, pyridine ring, pyrazine ring and pyrimidine ring.

28. Compounds or their pharmaceutically acceptable salts as set forth in Claim 17, in which Ar is a substituent selected from the group consisting of phenyl, 4-fluorophenyl, 3,4-difluorophenyl, 4-chlorophenyl, 4-methoxyphenyl, 4-tolyl, 4-trifluoromethylphenyl, pyridinyl, 6-fluoropyridin-3-yl, 6-trifluoromethylpyridin-3-yl, and 6-methoxypyridin-3-yl.

29. Compounds or their pharmaceutically acceptable salts as set forth in Claim 17, in which the compound represented by the general formula [I-1] is

- 2-(3,4-difluorophenyl)-2-(2-oxo-1-pyrrolidinyl)-N-[3-(spiro[5- fluoroisobenzofuran-1(3H), 4'-piperidin]-1-yl)propyl]acetamide,
- 2-(3,4-difluorophenyl)-N-methyl-2-(1H-1,2,3-triazol-1-yl)-N- [3-(spiro [isobenzofuran-1(3H), 4'-piperidin]-1-yl)propyl]acetamide,
- 2-(3,4-difluorophenyl)-N-methyl-2-(2H-1,2,3,4-tetrazol-2-yl)-N-[3-(spiro[isobenzofuran-1(3H), 4'-piperidin]-1-yl)propyl]acetamide,
- 2-(3,4-difluorophenyl)-N-methyl-2-(2-oxo-1(2H)pyridinyl)-N- [3-(spiro[isobenzofuran-1(3H), 4'-piperidin]-1-yl)propyl]acetamide,
- 2-(3,4-difluorophenyl)-N-methyl-2-(2-oxo-1- pyrrolidinyl)-N- [3-(spiro[5-fluoroisobenzofuran-1(3H),4'-piperidin]-1-yl)propyl]- acetamide,
- 2-(3,4-difluorophenyl)-N-methyl-2-(2-methyl-1H-imidazol-1-yl)-N-[3-(spiro[6-fluoroisobenzofuran-1(3H),4'-piperidin]-1-yl)propyl]-acetamide,
- 2-(3,4-difluorophenyl)-N-methyl-2-(2-methyl-1H-imidazol-1-yl)-N-[3-(spiro[5-fluoro-6-azaisobenzofuran-1(3H),4'- piperidin]- 1-yl)propyl]acetamide,
- 2-(3,4-difluorophenyl)-2,2-dimethyl-N-methyl-N-[3-(spiro[5-fluoro-6-azaisobenzofuran-1(3H),4'- piperidin]-1-yl)propyl]acetamide,

• 2,2-bis(6-fluoro-3-pyridinyl)-N-methyl-N-[3-(spiro[5-fluoro-6-azaisobenzofuran-1(3H),4'- piperidin]- 1-yl)propyl]acetamide,

• 2,2-bis(4-fluorophenyl)-N-methyl-N-[3-(spiro[5-fluoro-6-azaisobenzofuran-1(3H),4'- piperidin]- 1-yl)propyl]acetamide,

• 2-(3,4-difluorophenyl)-N-methyl-2-(1H-pyrrol-1-yl)-N-[3- (spiro[5-fluoro-6-azaisobenzofuran-1(3H),4'-piperidin]-1-yl)propyl]- acetamide,

• 2-(4-fluorophenyl)-N-methyl-2-(1H-pyrrol-1-yl)-N-[3-(spiro- [5-fluoro-6-azaisobenzofuran-1(3H),4'-piperidin]-1-yl)propyl]- acetamide,

• 2-(3,4-difluorophenyl)-N-methyl-2-(1H-pyrazol-1-yl)-N- [3-(spiro[5-fluoro-6-azaisobenzofuran-1(3H),4'- piperidin]- 1-yl)propyl]acetamide,

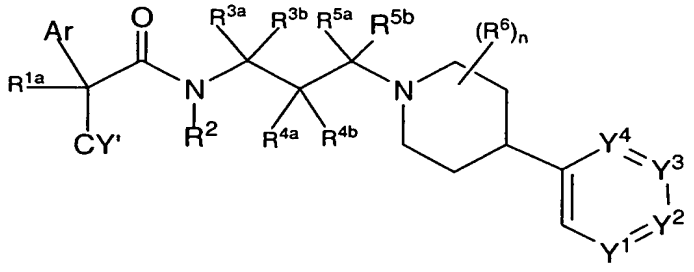
• 2-(3,4-difluorophenyl)-N-methyl-2-(1H-pyrrol-1-yl)-N- [3-(spiro[6-fluoro-5-azaisobenzofuran-1(3H),4'- piperidin]- 1-yl)propyl]acetamide,

• 2-(3,4-difluorophenyl)-N-ethyl-2-(2-oxo-1-pyrrolidinyl)-N- [3-(spiro[isobenzofuran-1(3H),4'-piperidin]-1-yl)propyl]acetamide,

• 2-(3,4-difluorophenyl)-N-ethyl-2-(4-methanesulfonyl)-2-oxo- 1-piperazinyl)-N-[3-(spiro[6-fluoroisobenzofuran-1(3H),4'-piperidin]- 1-yl)propyl]acetamide, or

• 2,2-bis(4-fluorophenyl)-2-hydroxy-N-methyl-N-[3-(spiro[5- fluoro-6-azaisobenzofuran-1(3H),4'- piperidin]-1-yl)propyl]acetamide,

30. Piperidine derivatives which are represented by the general formula [I-2]:

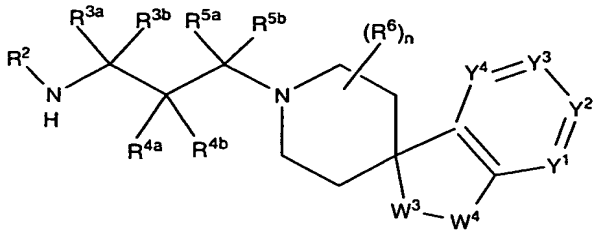


[I-2]

[in which R^{1a}, R^2, R^{3a}, R^{3b}, R^{4a}, R^{4b}, R^{5a}, R^{5b}, R^6, Y^1, Y^2, Y^3, Y^4, CY', Ar and n have the same significations as given in Claim 3] or their pharmaceutically acceptable salts.

31. Pharmaceutical preparations which comprise the compounds or their pharmaceutically acceptable salts as set forth in Claim 17 or the compounds or their pharmaceutically acceptable salts as set forth in Claim 30, and pharmaceutically acceptable carriers.

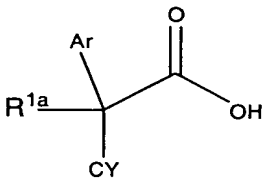
32. A method for producing a compound represented by the general formula [I-1], which comprises a step for amidating a compound represented by a general formula [IIa]:



[IIa]

[in which, R^2, R^{3a}, R^{3b}, R^{4a}, R^{4b}, R^{5a}, R^{5b}, R^6, Y^1, Y^2, Y^3, Y^4, W^3, W^4 and n have the same significations as given in Claim 2]

with a compound represented by a general formula (IIIa)



[IIIa]

[in which Ar, R^{1a} and CY have the same significations as given in Claim 2].